Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 10-12, 25-27, 40-42 and 58-63 are pending in the application, with claims 10, 25, 40, 58, 60 and 62 being the independent claims. Claims 13-15, 28-30, 43-45 and 55-57, drawn to non-elected subject matter, are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 58-63 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Support for Amended and New Claims

Support for amended claim 12 can be found, for example, in the specification at page 6, lines 3-5 and in original claim 12. Support for amended claim 27 can be found, for example, in the specification at page 7, lines 26-28 and in original claims 27. Support for amended claim 42 can be found, for example, in the specification at page 9, lines 10-12 and in original claim 42.

Support for new claims 58 and 59 can be found, for example, in the specification at page 5, line 28 through page 6, line 5 and in original claims 10-12. Support for new claims 60 and 61 can be found, for example, in the specification at page 7, lines 21-28 and in

original claims 25-27. Support for new claims 62 and 63 can be found, for example, in the specification at page 9, lines 6-12 and in original claims 40-42.

II. Claim Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 11 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. *See* Paper No. 10, page 2. According to the Office Action, "[c]laim 11 is rendered vague and indefinite by the phrase 'or a hydrophobic derivative thereof', which fails to make it clear what is meant by this phrase." *See* Paper No. 10, page 2.

Applicants first note that claim 11 does not recite the phrase "or a hydrophobic derivative thereof." This phrase is, however, found in claim 12[1]. Thus, it appears that the intended rejection under 35 U.S.C. § 112, second paragraph, was a rejection of claim 12, not a rejection of claim 11.

Although Applicants respectfully disagree with the basis of this rejection, claim 12 (as well as claims 27 and 42) has been amended to read: ". . . wherein the chelator is bathocuproine." None of the currently presented claims include the phrase "or a hydrophobic derivative thereof." Thus, the rejection under 35 U.S.C. § 112, second paragraph, has been fully accommodated and should be withdrawn.

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[1]Applicants note that the expression "or a hydrophobic derivative thereof" is also found in pending claims 27 and 42.

III. Claim Rejections Under 35 U.S.C. § 103

Claims 10-12, 25-27 and 40-42 were rejected under 35 U.S.C. § 103(a) as being unpatentable over "WIPO (AO2)" in view of "Gerolymatos (AB2)" (U.S. Patent No. 5,980,914, hereinafter "Gerolymatos"). *See* Paper No. 10, page 3. Applicants respectfully traverse this rejection.

As a preliminary matter, it is unclear which document "WIPO (AO2)" is intended to represent. The document designated AO2 in Applicants' Information Disclosure Statement (IDS) filed March 5, 2002 is International Patent Application WO 97/04794. Application WO 97/04794 does not appear to be the document that the Office Action intended to cite. First, the Office Action referred to the cited document as "Choi et al." *See* Paper No. 10, page 3; however, on the face of WO 97/04794, there is no applicant, inventor or agent referred to as "Choi." Second, the Office Action specifically pointed to page 2 of the cited document as supposedly (1) disclosing neurodegenerative disorders such as Alzheimer's disease, and (2) disclosing metal chelators such as EGTA, TPEN and TSQ. *See* Paper No. 10, page 3. At page 2 of WO 97/04794, however, neither Alzheimer's disease nor any of the above-listed metal chelators is recited. Therefore, it appears that the document cited in the Office Action as "WIPO (AO2)" is *not* the document that is designated AO2 in the IDS of March 5, 2002.

Applicants' undersigned representative has made repeated attempts[2] to contact the Examiner by telephone to determine which document "WIPO (AO2)" was intended to

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[2]Three voice-mail messages were left for the Examiner requesting clarification as to which reference "WIPO (AO2)" was intended to represent: one on July 31, 2002, one on August 6, 2002, and one on December 16, 2002.

represent. None of the attempts at contacting the Examiner were successful, and, as of the date indicated below, the messages that were left by the undersigned have not been returned.

Nevertheless, Applicants note that the document designated AP2 (not AO2) in the IDS of March 5, 2002 (WO 97/09976) lists Choi *et al.* as inventors. Applicants also note that the cited Gerolymatos reference makes reference to WO 97/09976. *See* Gerolymatos at column 2, lines 47-51. Thus, it appears that the document that the Examiner intended to cite in the rejection under § 103, in addition to Gerolymatos, was WO 97/09976.

Regardless of which document the Office Action intended to cite as "WIPO (AO2)," Applicants respectfully submit that a *prima facie* case of obviousness has not been established. In order to establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). In addition, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). The teaching or suggestion to make the claimed combination cannot be derived from Applicants' disclosure. *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Evidence of a suggestion, teaching, or motivation to combine references may flow, *inter alia*, from the references themselves, the knowledge of one of ordinary skill in the art, or from the nature of the problem to be solved. *See In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). Although a reference need not expressly teach that the disclosure contained therein should be combined with another, *see Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997), the showing of

combinability, in whatever form, must nevertheless be "clear and particular." *Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to Applicants' claims because there has not been an adequate showing of a motivation to combine the reference teachings. The Office Action does not point to any specific statement(s) or evidence in the cited references (or elsewhere) demonstrating that a skilled artisan would have been motivated to combine the reference teachings. Instead, the following explanation for the rejection is provided:

> WIPO, hereby known as Choi et al., teaches metal chelators to treat neurotoxic injuries, such as neurodegenerative disorders. Note page 2 discloses the neurodegenerative disorders, such as Alzheimer's disease. Page 2, lines 27-35 also teach the other metal chelators, such as EGTA, TPEN and TSQ . . .
>
> The instant invention differs from the cited reference [*i.e.*, "WIPO (AO2)"] in that the cited reference does not teach the addition of clioq[u]inol with the metal chelators to treat Alzheimer's disease. However, the secondary reference, Gerolymatos, teach clioquinol as a well-known agent to combine the two individual anti-amyloidosis (Alzheimer's disease) agents into a single composition and achieve the same results (an additive effect) in the absence of evidence to the contrary.

See Paper No. 10, pages 3-4. Applicants respectfully disagree with these contentions and note that, even if accurate, these assertion would not demonstrate a legally sufficient motivation to combine the reference teachings.

Applicants disagree with the Office Action's characterization of the Gerolymatos reference. Gerolymatos describes methods of treatment and prevention of Parkinson's

disease by administering clioquinol alone or in combination with vitamin B_{12}. *See* Gerolymatos at column 3, lines 13-15. Gerolymatos suggests that the mode of action of clioquinol is as an iron chelator which clears the accumulated iron observed in the brains of patients of Parkinson's disease. For Example, Gerolymatos states that "the aim of using a chelating agent such as clioquinol is to chelate or clear the iron that has been accumulated in the brain and, in particular, in the substantia nigra." *See* Gerolymatos at column 5, lines 37-40. There is no discussion in Gerolymatos of using clioquinol to treat amyloidosis specifically or Alzheimer's disease generally. Nor is there any discussion or suggestion in Gerolymatos to use clioquinol in combination with any other metal chelator(s).

Methods for treating or preventing Parkinson's disease would not provide any suggestion as to a method for treating or preventing Alzheimer's disease. Alzheimer's disease is a pathological state characterized by the acquired toxic properties of β-amyloid and the aggregation of insoluble amyloid. Importantly, Alzheimer's disease is differentiated from Parkinson's disease (PD) by the neurotoxic "target"protein involved; *i.e.*, β-amyloid and α-synuclein, respectively. These two diseases are also differentiated from one another by the types of metals implicated in the causation of the diseases. Gerolymatos implicates iron in Parkinson's disease. *See* Gerolymatos at column 5, lines 37-42. By contrast, in the present invention, copper and zinc are targets for chelation therapy. For example, the specification states:

> The discovery that Aβ can generate H_2O_2 and Cu^+, both of which are associated with neurotoxic effects, offers an explanation for the neurotoxicity of Aβ polymers. These findings suggest that it may be possible to lessen the neurotoxicity of Aβ by controlling factors which alter the concentrations of Cu^+ and ROS, including hydrogen peroxide, being generated by accumulated and soluble Aβ.

> It has been discovered that manipulation of factors such as zinc, copper, and pH can result in altered Cu^+ and H_2O_2 production by Aβ. Therefore, agents identified as being useful for the adjustment of the pH and levels of zinc and copper of the brain interstitium can be used to adjust the concentration of Cu^+ and H_2O_2, and can therefore be used to reduce the neurotoxic burden. Such agents will thus be a means of treating Alzheimer's disease.

Specification at page 21, lines 8-18. *See also* specification at page 95, lines 21-25 and at page 96, lines 9-11.

In addition, WO 97/09976 (assuming that this is the document that the Examiner intended to cite as "WIPO (AO2)"), does not mention clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) at all[3]. Nor does WO 97/09976 teach or suggest that any of the chelators disclosed therein could or should be combined with a chelator such as clioquinol.

The Examiner has not provided evidence in the Office Action indicating that a skilled artisan would be motivated to combine the reference teachings. With respect to claims 12, 27 and 42 (and new claims 59, 61 and 63) in particular, Applicants note that neither of the references cited in the Office Action (apparently) disclose bathocuproine. Regarding bathocuproine, The Office Action states:

> The instant invention differs from the cited reference [*i.e.*, "WIPO (AO2)"] in that the cited reference does not teach the applicants' preferred metal chelator, bathocuproine. However, one skilled in the art would have been highly motivated to substitute one metal chelator for another metal chelator that possess[es] the same activity to treat neurodegenerative disorders in the absence of evidence to the contrary.

See Paper No. 10, page 4.

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[3]WO 97/09976 is cited in the background of Gerolymatos, at column 2, lines 47-51, where it is stated that "[c]lioquinol has recently been shown to be effective in the treatment of . . . neurotoxic injury." This is an incorrect assertion by Gerolymatos. WO 97/09976 does not disclose clioquinol.

The foregoing statement is not legally sufficient to establish motivation to combine or modify the reference disclosures. "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221USPQ 929, 933 (Fed. Cir. 1984). The Office Action provides no support for the assertion that a person of ordinary skill in the art would regard clioquinol as "possess[ing] the same activity to treat neurodegenerative disorders." This is simply a conclusory statement that cannot be relied upon to support a rejection under 35 U.S.C. § 103. *See Rouffet*, 149 F.3d at 1357, 47 USPQ2d at 1457-58. Moreover, even if the statement in the Office Action regarding clioquinol's activity were accurate, the unsupported conclusion that "one skilled in the art would have been highly motivated to substitute one metal chelator for another metal chelator. . ." does not provide the "clear and particular" evidence that is required under relevant case law to establish a *prima facie* case of obviousness. *See Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. There must, at the very least, be some particular evidence presented that would indicate or suggest the combination in question.

In summary, there is no evidence presented in the Office Action that would indicate that a person of ordinary skill in the art would have been motivated to combine the cited reference teachings. A *prima facie* case of obviousness requires that there be clear and particular evidence presented that would indicate the desirability of the combination. It is therefore apparent that the rejection of claims 10-12, 25-27 and 40-42 under 35 U.S.C. § 103 was improper. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Specification:

At page 1, immediately after the title, please replace the paragraph and caption that were inserted into the specification (*See* Preliminary Amendment filed September 21, 2001) with the following:

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a divisional application of U.S. Patent Application No. 09/038,154, filed March 11, 1998, now U.S. Patent No. 6,323,218, issued November 27, 2001.

In the Claims:

Please cancel claims 13-15, 28-30, 43-45 and 55-57 without prejudice or disclaimer.

Please substitute the following claim 12 for the pending claim 12:

12. (Once amended) The method of claim 11, wherein the chelator is bathocuproine [or a hydrophobic derivative thereof].

Please substitute the following claim 27 for the pending claim 27:

27. (Once amended) The method of claim 26, wherein the chelator is bathocuproine [or a hydrophobic derivative thereof].

Please substitute the following claim 42 for the pending claim 42:

42. (Once amended) The pharmaceutical composition of claim 41, wherein the chelator specific for the reduced form of copper is bathocuproine [or a hydrophobic derivative thereof].

Please add claims 58-63.